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ORIGINAL ARTICLE

Optimal time interval between laparoscopic tubal ligation for hydrosalpinges and ICSI-ET☆

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KEYWORDS

Hydrosalpinx;
Tubal ligation;
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Abstract *Objective:* To determine the optimal time interval between performing laparoscopic tubal ligation for hydrosalpinges and an ICSI-ET treatment cycle.

Design: A retrospective cohort study.

Setting: Private infertility clinic.

Patient(s): The study group included 69 infertile women who had laparoscopic tubal ligation for hydrosalpinges. 41 patients (group A) had an ICSI-ET cycle < 10 weeks after laparoscopic tubal surgery, 20 patients (group B) had an ICSI-ET cycle 10 and 16 weeks after surgery, and 20 patients (group C) had an ICSI-ET cycle > 16 weeks after surgery.

Intervention(s): laparoscopic tubal ligation and ICSI-ET.

Main outcome measure(s): Pregnancy rate, clinical pregnancy rate and implantation rate.

Result(s): Pregnancy rates were 39%, 50% and 50%, clinical pregnancy rates 31.7%, 45% and 50%, and implantation rates 14.8%, 21.5% and 18% for groups A, B and C respectively.

Conclusion(s): Although the reduction in pregnancy rate, clinical pregnancy rate and implantation rate in Group A, as compared Groups B and C, did not reach statistical significance, our results suggest that ICSI-ET treatment cycles be postponed for at least 10 weeks after laparoscopic tubal ligation for hydrosalpinx. A larger prospectively randomized study should be conducted to confirm the minimum delay period required for endometrial receptivity to recover.

☆ In a retrospective cohort study, it was found that patients that had an ICSI-ET cycle within 10 weeks of a laparoscopic tubal ligation procedure for hydrosalpinges had impaired implantation and pregnancy outcomes compared to those who had an ICSI-ET cycle after 10 weeks. Postponing ICSI-ET treatment cycle for at least 10 weeks after the tubal ligation for hydrosalpinges may be beneficial to reproductive outcomes.

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1. Introduction

Tubal disease is one of the major indications for IVF. The etiology of the tubal factor infertility may, however, have a significant impact on patient fecundity. Hydrosalpinx associated tubal factor has been shown to be predisposed to the most impaired reproductive outcomes of the tubal factors. This has been inconclusively demonstrated by a number of studies that have shown a significant reduction in pregnancy rates and increase in pregnancy loss in patients with hydrosalpinges (1–8), especially in cases where the hydrosalpinges are large enough to be visible on ultrasound (8). The deleterious impact of hydrosalpinx on reproduction maybe as a direct result of the tubo-utero circulation of hydrosalpinx fluid, as the fluid has been linked to embryo cyto-toxicity, altered embryo–endometrium receptivity, and altered tubo-uterine flow dynamics (9–12,13,14).

With advances in assisted reproductive technologies (ARTs) it has become usual practice to attempt to treat these patients with IVF rather than to attempt to restore tubal function for natural conception. However, to accomplish this patients have to undergo permanent tubal sterilization procedures that block the tubo-utero connection and therefore the flow of hydrosalpinx fluid into the uterus. Numerous studies have inconclusively shown that surgical interventions such as tubal ligation or proximal tubal occlusion significantly improve assisted reproduction outcomes in IVF (15–18).

No studies have, however, investigated whether hydrosalpinx fluid has a lasting effect on the clinical aspects endometrial receptivity. The purpose of this retrospective cohort study was therefore to indirectly investigate the length of time needed for the uterine endometrium to recovery from the affects of hydrosalpinx by analyzing the pregnancy outcomes at different time periods post-tubal surgery.

2. Patients and methods

Patients who were diagnosed with hydrosalpinx-related tubal factor infertility with the use of transvaginal ultrasound or hysterosalpingography at Antalya IVF and who wished to pursue IVF were consulted on the need for and the implications of laparoscopic tubal ligation. All patients received counseling on the implications and risks of the procedures and informed consent was obtained before the therapeutic tubal procedures were scheduled to be performed. Patients excluded from further analysis were patients older than 42, patients with only one ovary, and patients with a basal FSH concentration of >12 IU/l. Eighty-one infertile patients who met the criteria underwent laparoscopic tubal ligation procedures for hydrosalpinges during the study period. Institutional ethics committee approval was received for the study.

Laparoscopic uni- or bilateral tubal ligation procedures were performed as ambulatory procedures at Antalya IVF. Laparoscopic tubal ligation was performed by bipolar cautery of affected tubes at the proximal position followed by the cutting of the tube at the coagulated area, leaving the cut tube in place. Two hours post-operatively all patients were assessed before being discharged.

All patients at Antalya IVF undergo ICSI-ET cycles. Controlled ovarian stimulation (COS) was performed using a GnRH agonist protocol, with the administering of luteal Gn-RH agonist (Leuprolide acetate; Lucrin daily, Abbott, Turkey) and recombinant gonadotropins (Gonal F; Serono, or Puregon; Organon). An hCG (Ovidrel, Merck Serona, 250 μg/0,05 ml) trigger was administered when at least three follicles reached 17 mm in diameter. Transvaginal ultrasound-guided oocyte retrieval was performed 36 h after ovulation induction. Retrieved oocytes were denuded and all mature oocytes were fertilized by ICSI. All embryo replacements were performed on day 2 of embryo development. Embryos were graded on a scale of 1–4 (1 being best) based on cell number, blastomere size and equivalence, and percentage of fragmentation (19). The luteal phases of all cycles were supplemented with E2 (Estrofem, Novo Nordisk, 2 mg BD) and P4 (Crınone, Merck Serono, 8% BD) and continued for at least 9 weeks of gestation if pregnant.

The patients were divided into three groups according to interval in weeks between laparoscopic tubal ligation and ICSI-ET treatment; group A included all patients that had ICSI-ET cycles <10 weeks after laparoscopic surgery, group B included all patients that had ICSI-ET cycles 10 to16 weeks after surgery and group C included all patients that had ICSI-ET cycles >16 weeks after surgery.

2.1. Statistical analysis

Age, percentages of patients over 37 years of age, bilaterality, antral follicle count, length of infertility, day 3 FSH, peak E2 levels, days of stimulation, total rFSH dosage, total oocytes retrieved, M2 oocytes retrieved, number of embryos transferred, number of grade 1-embryos transferred, pregnancy rate (positive HCG), clinical pregnancy rate (positive fetal cardiac activity), and implantation rate were compared between the groups. ANOVA and Chi-square test were used for statistical comparisons. $P < 0.05$ was considered statistically significant. Statistical calculations were performed using Sigmastat for Windows, version 3.0 (Jardel Scientific Corporation, San Rafael, CA).

3. Results

Forty-one patients (group A) had ICSI-ET cycles <10 weeks after laparoscopic surgery, 20 patients (group B) had ICSI-ET cycles 10 to16 weeks after surgery and 20 patients (group C) had ICSI-ET cycles >16 weeks after surgery.

The demographical characteristics and reproduction outcomes of the 3 patient groups are presented and described in Table 1. No statistically significant differences were found between the demographic and reproductive variables of age, bilaterality, antral follicle count, day 3 FSH, peak E2 levels, days of stimulation, total rFSH dosage age, total oocytes retrieved, MII oocytes retrieved, number of embryos transferred, number of grade 1-embryos transferred, between the 3 groups.

The pregnancy outcomes for groups A, B, and C were as follows; positive βhCG pregnancy (39.0 vs 50 vs 50; $p = 0.610$), clinical pregnancy rate (31.7 vs 45.0 vs 50.0; $p = 0.330$), and implantation rate (14.8 vs 21.5 vs 18.0; $p = 0.420$). Although not significant all the parameters in group A were reduced compared to groups B and C, while outcomes between groups B and C were very similar.

4. Discussion

Tubal disease is one of the major causes of female infertility (20). IVF-embryo transfer was initially developed as a method to overcome tubal infertility (21). IVF-embryo transfer studies examining reproductive outcomes in tubal disease patients reported particularly low pregnancy and implantation rates in patients with hydrosalpinx associated tubal disease (5,7,8). Therapeutic studies have shown that with appropriate surgical intervention in vivo fecundity in affected patients can be improved (3,17), as well as in vitro fecundity, conclusively demonstrated in a prospective, randomized multicentre trial to measure the benefit of tubal surgical intervention prior to IVF on clinical reproductive outcomes (15).

Direct embryotoxic effects (9), physical interference due to the intrauterine accumulation of refluxed fluid (14), and an altered endometrial receptivity (13) are among some of the proposed pathological mechanisms by which hydrosalpinx impairs intrauterine embryo development, embryo implantation and pregnancy development.

Lessey et al. (22,23) and Tabibzadeh (24) evaluated the expression of integrin molecules by human endometrium throughout the menstrual cycle. The vitronectin receptor, $\alpha_V\beta_3$, was found to appear abruptly on cycle day 19 or 20, coincident with the opening of the putative implantation window. The expression of $\alpha_V\beta_3$ was absent in endometrial biopsies taken on these days when there was maturational delay. $\alpha_V\beta_3$ integrin may therefore serve as an important internal marker for luteal phase maturation and endometrium receptivity (22,23). Meyer et al. (13) documented endometrial dysfunction in patients with hydrosalpinges, with the histological samples of affected patients exhibiting signs of maturational delay and lower integrin expression levels. Furthermore Lessey et al. (23) demonstrated in their study that tubal corrective surgery in patients with confirmed tubal hydrosalpinges and concomitant reduced $\alpha_V\beta_3$ expression had $\alpha_V\beta_3$ expression levels return to normal 3 months post-operatively. Similarly, Bildirici et al. (25) demonstrated a significant increase in $\alpha_V\beta_3$ integrin expression following salpingectomy and therefore argued that this increased expression would be indicative of improved endometrial receptivity.

Our study was therefore initiated to test the hypothesis that a period of at least 3 months post-operatively was required for endometrial receptivity to recover from the effects of hydrosalpinx. The key objective being to determine the minimum length of time required to allow the complete wash-out of the hydrosalpinx related effects on clinical pregnancy outcomes following tubal surgery. In our study period 81 patients were found that had tubal ligations for uni- or bilateral hydrosalpinx, because of their wish to have assisted reproductive treatment. The ICSI-ET treatment cycles performed for these patients were categorized according to 3 delay intervals (<10 weeks, 10–16 weeks and >16 weeks) between surgery and treatment and the inter-category reproductive outcomes compared. The results of the study show that a minimum 10 week wash-put period should be allowed for, as patients treated within this period had reduced reproductive outcomes as compared to the patients treated after 10 weeks. The results of our clinical study corroborates the evidence found in the integrin expression studies, that there is a time-dependent delay of at least 10 weeks for the endometrial development and function to normalize after the removal of the effects of hydrosalpinx.

The results from our retrospective study are unfortunately only strongly suggestive of improved reproductive outcomes, if ICSI-ET treatment was performed at least 10 weeks after laparoscopic surgery for hydrosalpinx, as the differences in reproductive outcomes did not reach statistical significance. The outcomes of this study and those of the integrin expession studies do, however, suggest that a larger prospectively randomized study is warranted to confirm the minimum delay period required for the endometrium to recover from the effects of hydrosalpinx.

Table 1 Demographic features and clinical outcomes.

	Group A <10 weeks	Group B 10–16 weeks	Group C >16 weeks	*p*-Value
No. patients (n)	41	20	20	NA
Age (yrs)	32.8 ± 0.6	33.6 ± 0.8	32.9 ± 0.8	0.709
Length of infertility (yrs)	7.5 ± 0.6	6.5 ± 0.6	7.1 ± 0.8	0.583
Bilateral tubal occlusion (%)	36.5	40.0	40.0	0.951
No. Antral follicles (n)	13.2 ± 0.9	13.9 ± 1.2	13.3 ± 1.1	0.892
Day 3 FSH (IU/mL)	6.9 ± 0.6	7.2 ± 0.8	6.9 ± 0.7	0.950
Peak E2 levels (pg/ml)	1605 ± 405	1780 ± 350	1780 ± 350	0.963
Days of stimulation (n)	8.8 ± 0.2	9.5 ± 0.3	9.0 ± 0.4	0.258
FSH ampoules (n)	53.1 ± 3.4	48.1 ± 5.9	58.4 ± 4.1	0.356
Oocytes collected (n)	13.7 ± 0.9	14.6 ± 1.7	12.8 ± 1.1	0.665
MII oocytes collected (n)	9.8 ± 0.8	9.8 ± 1.4	9.3 ± 1.2	0.952
Embryos transferred (n)	2.3 ± 0.1	2.0 ± 0.3	2.5 ± 0.4	0.414
Grade 1 embryos (n)	2.0 ± 0.2	1.8 ± 0.3	2.2 ± 0.3	0.629
Pregnancy rate (%)	39.0	50.0	50.0	0.610
Clinical pregnancy rate (%)	31.7	45.0	50.0	0.330
Implantation rate (%)	14.8	21.5	18.0	0.420

Note: values are mean ± SEM.

Conflict of interest

We have no conflict of interest to declare.

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